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Risk stratification of normotensive pulmonary embolism: One more ride on the merry-go-round

Luca Valerio[1] and Stefano Barco[1,2]

Risk stratification is central to the management of normotensive patients with haemodynamically stable acute pulmonary embolism. By assigning each patient to a specific risk class, the physician is guided in the choice of the most appropriate management modality, including but not limited to the timing, type and setting of treatment.[1,2]

At the high end of the severity spectrum, treatment of pulmonary embolism is aimed to minimize the risk of haemodynamic deterioration and to prevent death. The management of these patients rests on close monitoring, ideally in a higher-intensity setting, as they may need advanced reperfusion therapies if the situation escalates. At the opposite end are patients at the lowest risk of early death. In the foreground, in this case, is the maximization of the patient's satisfaction and quality of life, as well as reasonable governance of health resources. If all requirements for their safety are met, these patients can be considered for early discharge and home anticoagulant treatment. An overview of these points is provided in Figure 1.

The 2019 update of the pulmonary embolism guidelines of the European Society of Cardiology (ESC), developed in cooperation with the European Respiratory Society, reinforced the concept that the two pillars of risk stratification are the pre-existing health status, i.e. the presence of major comorbidities, and the severity of pulmonary embolism itself.[3] Together, they allow clinicians to estimate the individual patient's potential to deteriorate despite apparent initial haemodynamic compensation. Comorbidities may independently increase the individual risk of death or affect the capacity for haemodynamic compensation. The severity of pulmonary embolism itself is reflected by the degree of haemodynamic compromise that vascular obstruction causes.

In this issue of the *European Heart Journal – Acute Cardiovascular Care*, readers will find four studies contributing valuable information on key risk stratification concepts covering almost the whole spectrum of pulmonary embolism severity.[4–6] The low-risk end of the spectrum was addressed by studies that updated or expanded the Pulmonary Embolism Severity Index, the most widely used tool for the identification of potential candidates for home treatment and low-intensity care. Yamashita et al. found that patients from the COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism (COMMAND VTE) registry with a simplified Pulmonary Embolism Severity Index ((s)PESI) of zero, indicating low-risk category, had a reasonably low 30-day mortality: two patients out of 383 (0.5%) died due to fatal pulmonary embolism and intracranial haemorrhage, respectively.[5] Vedovati and colleagues showed that the use of the respiratory index, the ratio of oxygen saturation in air to respiratory rate, may help to better identify higher-risk patients at risk of imminent decompensation and death.[4] They also confirmed that the observed 30-day mortality rate among patients with (s)PESI=0 was equally low (0.5%) and further minimized (0%) after exclusion of patients with signs of right ventricular dysfunction according to the latest 2019 ESC guidelines. This is in line with the conclusions of a recent systematic review and meta-analysis[7] showing that patients with (s)PESI denoting low-risk or, alternatively, the absence of all Hestia criteria are characterized by very low rates of pulmonary embolism-related complications and early deaths, but that only patients without signs of right ventricular dysfunction were characterized by a rate of complications that was close to zero.

Other studies addressed the challenges posed by intermediate and intermediate-high risk patients. Santos et al. reported that, in intermediate-high risk patients with signs of right ventricular dysfunction on echocardiography and/or computed tomographic angiography, the elevation of both troponin I and N-terminal pro-brain natriuretic peptide

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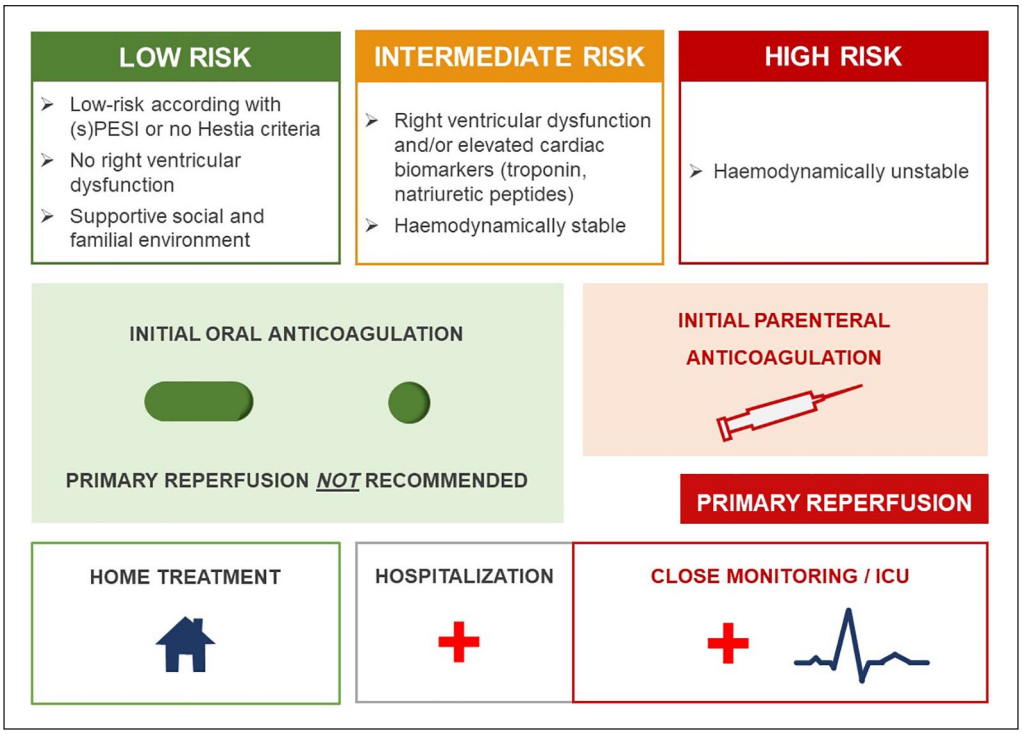

Figure 1. Risk stratification of patients with acute pulmonary embolism: key elements in the year 2020.
Validated clinical tools to identify low-risk patients with pulmonary embolism include the (simplified) Pulmonary Embolism Severity Index ((s)PESI) and the Hestia criteria. Haemodynamic instability at presentation is defined in the presence of a systolic blood pressure $<$90 mm Hg, or a drop by $\geqslant$40 mm Hg, for $>$15 min, not caused by new arrhythmia, hypovolaemia, sepsis. The figure was adapted and modified from the Illustrated State-of-the-Art Capsules prepared by the speakers of the International Society on Thrombosis and Haemostasis 2019 Congress.[16] ICU: intensive care unit.

was more strongly associated with all-cause or pulmonary embolism-related mortality and rescue thrombolysis than the elevation of either cardiac biomarker alone.[8] Similarly, the single-centre study by Novicic et al. found that the early resolution of specific ECG signs present at admission in 110 intermediate-high and high-risk patients were associated with better 30-day survival and lower right ventricular systolic pressure at discharge.[6]

Several cohort studies from the past decade focused on disease-specific and comorbidity-oriented parameters that are strongly associated with early complications after acute pulmonary embolism.[9] Most of these parameters are pathophysiologically and clinically interrelated: therefore, it does not come as a surprise that different markers of cardiopulmonary function are equally good at predicting the course of disease. The studies published in the *European Heart Journal – Acute Cardiovascular Care*[4–6] remind us that pulmonary embolism is a multifaceted condition and a comprehensive assessment of organ function, clinical parameters and demographic characteristics may also translate into a better risk stratification.

Are we experiencing the final round of this type of exploratory research focusing on novel parameters, or their combinations into models, for risk stratification of acute pulmonary embolism? In the literature there is a worrying abundance of successful prediction models and classifiers. In most cases, their conclusions have indicated that they may provide some type of benefit compared with prior ones simply because they asked too much of the available data, possibly leading to overfitting and overly optimistic estimates. Only a few studies investigated the impact of the implementation of specific models or parameters to drive clinical practice. Ideally, this should be tested in terms of clinical effectiveness, feasibility and costs. The interventional setting would allow for evaluation of whether the classification of patients into a risk category truly corresponds to a specific risk class and, ultimately, if an intervention chosen accordingly can improve their outcome.

A successful example of this process was the assessment of scores or combination of criteria designed to identify low-risk patients with acute pulmonary embolism who should be considered for early discharge and ambulatory anticoagulant treatment.[1,2] After their development in carefully designed and preferentially multi-centre observational studies not unlike those presented in this issue,[10] ad-hoc management studies or randomized controlled trials[11–14] led to the updated recommendations of international guidelines.[3] Ongoing research (Clinical Trials identifiers NCT02811237, NCT03002467) is testing whether the spectrum of patients who may be considered for outpatient management can be further expanded. In the very near future, physicians will be able to decide on home treatment

of acute pulmonary embolism based on validated treatment schemes and scores, adopting those that better suit the care setting where they operate.

In the next ride on the merry-go-round, we will hopefully witness the evaluation of novel, and possibly safer, reperfusion strategies for selected normotensive patients at a higher risk of decompensation.[1,2,15] This zone of the severity spectrum now represents the highest-priority point of the research agenda and may have profound impact on defining the standard of treatment of acute pulmonary embolism.

Conflict of interest

Stefano Barco reports personal fees from Biocompatibles Group UK, LeoPharma and Bayer HealthCare, non-financial support from Bayer HealthCare and Daiichi Sankyo, and an institutional grant from Sanofi, outside the submitted work. Luca Valerio has no conflicts of interest to declare.

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